Organ Transplantation in the Weeds: The Impact and Ethics of Marijuana Use

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Disclosures

- No financial disclosures or conflicts of interest.
Objectives & agenda

• Enhance liver clinicians’ understanding of marijuana’s complex intersection with liver disease and organ transplantation
  – Background
  – Epidemiology
  – Pharmacology
  – Legalization
  – Indications, risks, & benefits

• Raise *many more* questions than provide definitive answers
The distinction between diseases of "brain" and "mind," between "neurological" [and “medical”] problems, and "psychological" or "psychiatric" ones, is an unfortunate cultural inheritance that permeates society and medicine.

It reflects a basic ignorance of the relation between brain and mind.

We're transplanting humans, not angels.

James Neuberger
Associate Director
National Health Service Blood & Transport

Quoted in The Guardian 4/3/14: Heavy drinkers to be considered for NHS liver transplants
Background
Human history

- **Cannabis** genus of flowering plants
  - mainly comprised of *sativa* and *indica* species
- Indigenous to Central and South Asia
- For millennia, used for
  - rope, clothing, bowstrings, paper (hemp fiber)
  - seeds and seed oils
  - livestock feed
  - medicine
  - religious ceremonies
  - recreation

Epilepsia. 2014 Jun;55(6):791-802
U.S. history

- First criminalized - Marihuana Tax Act of 1937
  - Gov’t response to societal concerns about MJ prevalence and ills
- Nixon era - Controlled Substances Act of 1970
  - MJ became Schedule I
    - “no currently accepted medical use and a high potential for abuse”
- California – Compassionate Use Act of 1996
  - 1st state to legalize medically
- Medical marijuana is legal >50% of states
- Recreationally legal in 11 states
- Texas: Medical MJ with THC<0.5%
  - May 2019: recent expansion to Parkinson’s, ALD, autism, MS, cancer
Epidemiology
Epidemiology

- Most common “illicit” drug in the US
- ~12% of US people ages 12+ used MJ in the past year
- In 2015, >11 million young adults ages 18 to 25 used marijuana in the past year
- \( \downarrow \) number of young people who view regular marijuana use as risky
- General population rate of MJ use disorder in 2013 was 2.9%

https://www.drugabuse.gov/publications/drugfacts/marijuana
Pharmacology
THC pharmacology

- THC (Δ⁹-tetrahydrocannabinol)
  - Active at CB1 (CNS) and CB2 (immune) receptors
  - Rapid serum peak (3-8 min) & short half-life (30 min)
  - Metabolite persists 20-300 hrs depending on use
    - lipophilic
- ↑ CNS dopamine similar to other addictive substances
- endocannabinoids (anandamide, 2-AG)
  - metabolic function, inflammation, bone mass, antitumor properties, vasoregulation, lipogenicity
• Lower activity at the CB1 and CB2 receptors
  – 5-HT, glycine
• ↓ THC-related *Cannabis* side effects
• Low abuse potential
• Antiepileptic, anti-inflammatory, neuroprotective
• ↓ high quality data compared to widespread use

*Cannabidiol (CBD)*

Epilepsia. 2014 Jun;55(6):791-802
British journal of pharmacology, 153(2), 199-215.
Rx cannabinoids

- Antiemetic, appetite stimulant, analgesic
- dronabinol (Marinol), nabilone (Cesamet)
  - Schedule III ("moderate/low physical dependence or high psychological dependence")
- 1:1 THC / cannabidiol (Sativex)
  - approved for MS spasticity in Canada, UK
- cannabidiol (Epidiolex)
  - Lennox-Gastaut, Dravet syndromes; rare, severe epilepsy
- rimonabant
  - CB1 inverse agonist for appetite suppression
  - withdrawn in 2008 for psych side effects

Legalization
Colorado data – legal era

• ↑ healthcare utilization, MJ tourism, ED visits
• ↑ unintentional pediatric exposures
• ↑ 5x psych dx in ED MJ-related encounters than non-MJ
• ↑ MJ-related poison control center calls

• Direct
  – psychosis, depression, anxiety, delirium, insomnia, cyclic vomiting, child overdose (edibles), nonspecific medical symptoms

• Indirect
  – burns, other drug use, MVA

Monte et al. JAMA. 2015 Jan 20;313(3):241-2
Wang GS et al. JAMA pediatrics. 2016 Sep 1;170(9):e160971-.
Increases in THC Potency and ED visits

- National Drug Enforcement Administration seizure data

- Only marijuana associated with significant increases over time

- 62% increase in combination with other drugs, 100% increase used alone, P<0.05

Indications, Risks, and Benefits
52yo male with decompensated alcohol-related cirrhosis with 9 months sobriety, the longest of his life, referred for OLT eval.

His chronic narcotic regimen was recently successfully tapered by PCP. Now with a medical MJ card, smoking daily with adequate analgesia.
## Legal medical indications

<table>
<thead>
<tr>
<th>State</th>
<th>Legislation</th>
<th>Legal Indications</th>
</tr>
</thead>
<tbody>
<tr>
<td>California</td>
<td>Compassionate Use Act (Ballot Proposition 215) of 1996</td>
<td>Cancer, anorexia, AIDS, chronic pain, spasticity, glaucoma, arthritis, migraine, persistent muscle spasms, seizures, or any other illness for which marijuana provides relief</td>
</tr>
</tbody>
</table>
| Michigan  | Michigan Medical Marihuana Act 2008              | Cancer, glaucoma, positive status for human immunodeficiency virus, acquired immune deficiency syndrome, hepatitis C, amyotrophic lateral sclerosis, Crohn's disease, agitation of Alzheimer's disease, nail patella, or the treatment of these conditions.  
A chronic or debilitating disease or medical condition or its treatment that produces 1 or more of the following: cachexia or wasting syndrome; severe and chronic pain; severe nausea; seizures, including but not limited to those characteristic of epilepsy; or severe and persistent muscle spasms, including but not limited to those characteristic of multiple sclerosis |
| New York  | Compassionate Care Act of 2014                  | Cancer, HIV infection or AIDS, amyotrophic lateral sclerosis (ALS), Parkinson's disease, multiple sclerosis, spinal cord injury with spasticity, epilepsy, inflammatory bowel disease, neuropathy, Huntington's disease, post-traumatic stress disorder or chronic pain.  
The severe debilitating or life threatening condition must also be accompanied by one or more of the following associated or complicating conditions: cachexia or wasting syndrome, severe or chronic pain, severe nausea, seizures, or severe or persistent muscle spasms |
## Current & potential uses

<table>
<thead>
<tr>
<th>Category</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chronic pain</td>
<td>↓pain, anti-inflammatory, ?fewer opioid-related deaths in states with liberal MJ laws</td>
</tr>
<tr>
<td>GI</td>
<td>↓nausea, ↑appetite, inflammatory bowel disease treatment</td>
</tr>
<tr>
<td>Neurology</td>
<td>Antiepileptic, multiple sclerosis muscle spasticity, neuropathy</td>
</tr>
<tr>
<td>Psychiatry</td>
<td>PTSD</td>
</tr>
<tr>
<td>Organ transplantation</td>
<td>Graft-versus-host disease, ischemia &amp; reperfusion injuries</td>
</tr>
</tbody>
</table>

Possible adverse effects

| Table 1. Adverse Effects of Short-Term Use and Long-Term or Heavy Use of Marijuana. |
| Effects of short-term use |
| Impaired short-term memory, making it difficult to learn and to retain information |
| Impaired motor coordination, interfering with driving skills and increasing the risk of injuries |
| Altered judgment, increasing the risk of sexual behaviors that facilitate the transmission of sexually transmitted diseases |
| In high doses, paranoia and psychosis |
| Effects of long-term or heavy use |
| Addiction (in about 9% of users overall, 17% of those who begin use in adolescence, and 25 to 50% of those who are daily users) |
| Altered brain development |
| Poor educational outcome, with increased likelihood of dropping out of school |
| Cognitive impairment, with lower IQ among those who were frequent users during adolescence |
| Diminished life satisfaction and achievement (determined on the basis of subjective and objective measures as compared with such ratings in the general population) |
| Symptoms of chronic bronchitis |
| Increased risk of chronic psychosis disorders (including schizophrenia) in persons with a predisposition to such disorders |

* The effect is strongly associated with initial marijuana use early in adolescence.
## Confidence in the evidence

**Table 2. Level of Confidence in the Evidence for Adverse Effects of Marijuana on Health and Well-Being.**

<table>
<thead>
<tr>
<th>Effect</th>
<th>Overall Level of Confidence*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Addiction to marijuana and other substances</td>
<td>High</td>
</tr>
<tr>
<td>Abnormal brain development</td>
<td>Medium</td>
</tr>
<tr>
<td>Progression to use of other drugs</td>
<td>Medium</td>
</tr>
<tr>
<td>Schizophrenia</td>
<td>Medium</td>
</tr>
<tr>
<td>Depression or anxiety</td>
<td>Medium</td>
</tr>
<tr>
<td>Diminished lifetime achievement</td>
<td>High</td>
</tr>
<tr>
<td>Motor vehicle accidents</td>
<td>High</td>
</tr>
<tr>
<td>Symptoms of chronic bronchitis</td>
<td>High</td>
</tr>
<tr>
<td>Lung cancer</td>
<td>Low</td>
</tr>
</tbody>
</table>

*The indicated overall level of confidence in the association between marijuana use and the listed effects represents an attempt to rank the strength of the current evidence, especially with regard to heavy or long-term use and use that starts in adolescence.

Transplant waitlist survival

- 585 listed adults for OLT over 2 years
- MJ use prevalence 48%, 7% recent and 41% prior
- MJ associated with
  - ALD, HCV, smoking, alcohol and illicit drug use
- Not associated with
  - probability of OLT
  - waitlist mortality/delisting

Post-liver transplant mortality

- 1489 OLT patients
- MJ users:
  - younger; male; ↑HCV; ↓MELD; ↑narcs, benzos, barbs, stimulants
- No difference in race, alcohol screens, or psych background
- No effect on post-txp survival
- Covariates associated with mortality:
  - age, MELD, HCV status, transplant itself

### Decreased opioid deaths?

<table>
<thead>
<tr>
<th><strong>Bachhuber et al 2014</strong></th>
<th><strong>Shover et al 2019</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td>• Analysis of medical MJ laws and state-level death data of all 50 states 1999 - 2010</td>
<td>• Same methodology</td>
</tr>
<tr>
<td>• States with medical MJ laws had a 25% lower mean annual opioid overdose mortality rate compared to states without</td>
<td>• Extended analysis – 2017</td>
</tr>
<tr>
<td>• Effect strengthened over time post-legalization</td>
<td>• Reversed direction to +23% and remained positive after accounting for recreational cannabis laws</td>
</tr>
<tr>
<td></td>
<td>• No evidence that either permissive or restrictive laws associated with mortality</td>
</tr>
<tr>
<td></td>
<td>• Bachhuber = spurious</td>
</tr>
</tbody>
</table>

Bachhuber et al. JAMA Intern Med. 2014 Oct;174(10)
Shover et al. (2019). PNAS 16(26): 12624-12626
Immunosuppression & drug interactions

- Invasive *pulmonary aspergillosis* in immunocompromised patients
- Cannabinoids have *immunosuppressant* properties
- Tacrolimus toxicity
  - 67yo stem cell txp recip taking edible THC inpatient developed diarrhea, body stiffness, tremors, and altered mental status requiring ICU admission
  - 48yo OLT recip with agitated delirium POD #5 tacro level 17.2 from oral lozenges (10mg THC / 1mg CBD)
  - 32yo with epilepsy on tacro for interstitial nephritis entered CBD clinical trial (max 2900mg daily) and tacro levels increased by 3x with ↑Cr 2.4
What is a substance use disorder?

- Loss of control
- Severe psychosocial consequences
- Loss of function
- Physiological dependence

- Chronic brain changes
  - Reward, emotions, decision-making, cognition, behavior patterns
- Genetic, developmental, environmental etiologies
- “Choice” and “moral failing” → stigma

Substance use disorder risk

- 9% of those who experiment with marijuana will become addicted (using DSM criteria)
  - Increases to 1 in 6 among those who started as teenagers and to 25-50% among those who smoke daily
- Cannabis withdrawal syndrome
  - Irritability, sleeping difficulties, dysphoria, craving, anxiety
  - Cessation can be difficult and lead to ongoing relapse

Potentially combustible discussions

- Subjectivity
- Stigma
- Counter-transference
- Risk
- Emotional topics
- Uncertainty
- Team Respect / Trust

(MICHIGAN MEDICINE UNIVERSITY OF MICHIGAN)
OHSU proposed algorithm

Start
Liver transplant evaluation includes comprehensive assessment of substance abuse in candidate

Substance abuse problem identified

Unacceptable post-LT compliance risk
Combination of:
1. High risk of recidivism
2. Significant psychiatric co-morbidity
3. Poor social situation
   a. Unstable living environment
   b. Unacceptable support network

Decline for LT listing

Acceptable post-LT compliance risk
1. No significant psychiatric co-morbidity
2. Good social situation
   a. Stable living environment
   b. Good support network

Stop all addictive substance unless strong clinical indication exists as determined by team
- Marijuana, opiates, benzos.

List for transplant
After recommended period of abstinence and rehab/recovery if indicated
- Monitor for recidivism

No substance abuse problem

List for transplant if otherwise appropriate
Medical or recreational marijuana use NOT monitored

Factors used to diagnose Substance Use Disorder
1. Continued used despite repeated negative consequences
2. Multiple attempts to stop use, including rehabilitation attempts
3. Inability to stop use despite stated desire to do so
4. Little or no insight that substance use has led to negative consequences
Policies at different liver centers

• Survey of 100 UNOS-accredited programs
  – 49 responded
  – ≥2 from all regions

• 14% transplant active MJ users
  – additional 28% list if MJ is stopped

• More programs exclude recreational MJ than methadone

### TABLE 2.
Summary of alcohol, marijuana, and methadone policies among liver transplant programs

<table>
<thead>
<tr>
<th>Policies</th>
<th>Percent of responding programs</th>
</tr>
</thead>
<tbody>
<tr>
<td>Require 6-month alcohol abstinence</td>
<td>41</td>
</tr>
<tr>
<td>Waive 6-month alcohol abstinence for patients with AAH</td>
<td>69</td>
</tr>
<tr>
<td>Require alcohol and drug abstinence contract</td>
<td>76</td>
</tr>
<tr>
<td>Completion of formal rehabilitation for patients with history of alcohol/substance abuse</td>
<td>94</td>
</tr>
<tr>
<td>Random toxicology testing</td>
<td>69</td>
</tr>
<tr>
<td>Use of validated instrument to determine risk of relapse</td>
<td>21</td>
</tr>
<tr>
<td>Exclude methadone use</td>
<td>55</td>
</tr>
<tr>
<td>Exclude medical marijuana use</td>
<td>40</td>
</tr>
<tr>
<td>Exclude recreational marijuana use</td>
<td>72</td>
</tr>
</tbody>
</table>

MJ perceptions in heart transplant

360 transplant providers surveyed from 26 countries
Ethical Considerations
Principles of medical ethics

- **Autonomy**: individuals act intentionally, with understanding, and without controlling influences
- **Beneficence**: promote patient welfare and remove harm
- **Non-maleficence**: “do no harm” by acts of omission or commission
- **Justice**: people are equal and resources should be fairly allocated
Autonomy

• How should transplant providers protect a patient’s choice to use marijuana?

• Are there primary or secondary effects of marijuana that impact a patient’s autonomy?

• Should a patient’s SUD history and/or risk limit their choice to use marijuana as a transplant candidate or recipient?
Beneficence

- In end-stage disease and transplant, how do we balance the benefits of marijuana with its harms?

- Is it a transplant provider’s job to decide if marijuana is in a patient’s best interest?

- Does the prohibition and withdrawal of marijuana from a benefitting patient violate beneficence?
Non-maleficence

• Are we imposing harm by allowing marijuana in end-stage disease and transplant without robust evidence for its use?

• Should we be preferentially using approved, alternative Rx before marijuana?

• How will we know if marijuana is causing harm in end-stage disease and transplant patients?
Justice

• Should marijuana use impact a patient’s access to specialty medical care and transplantation? In SUD patients?

• Allocating organs, is it ethical to prioritize an abstaining patient over one who uses when other variables are similar?

• Should the legality of marijuana affect the allocation of an organ?
Conclusions
Conclusions

• Marijuana and cannabinoids are dynamic social, legal, and medical issues with a wide array of effects on patients and populations

• The cannabinoid system likely has substantial untapped therapeutic potential

• Marijuana exerts variable effects on organ function and pathology

• Marijuana has not been shown to directly impact transplant mortality though has some concerning risks

• Organ transplantation will continue to struggle with this complex issue due to lagging science, heterogeneous policies, and stigma
Thank you.

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